

図 5-6 肝内胆管がん、胆のうがん、肝外胆管がん外科治療内訳（男女計）：1993-2005 年診断例 新発生届出患者 大阪府

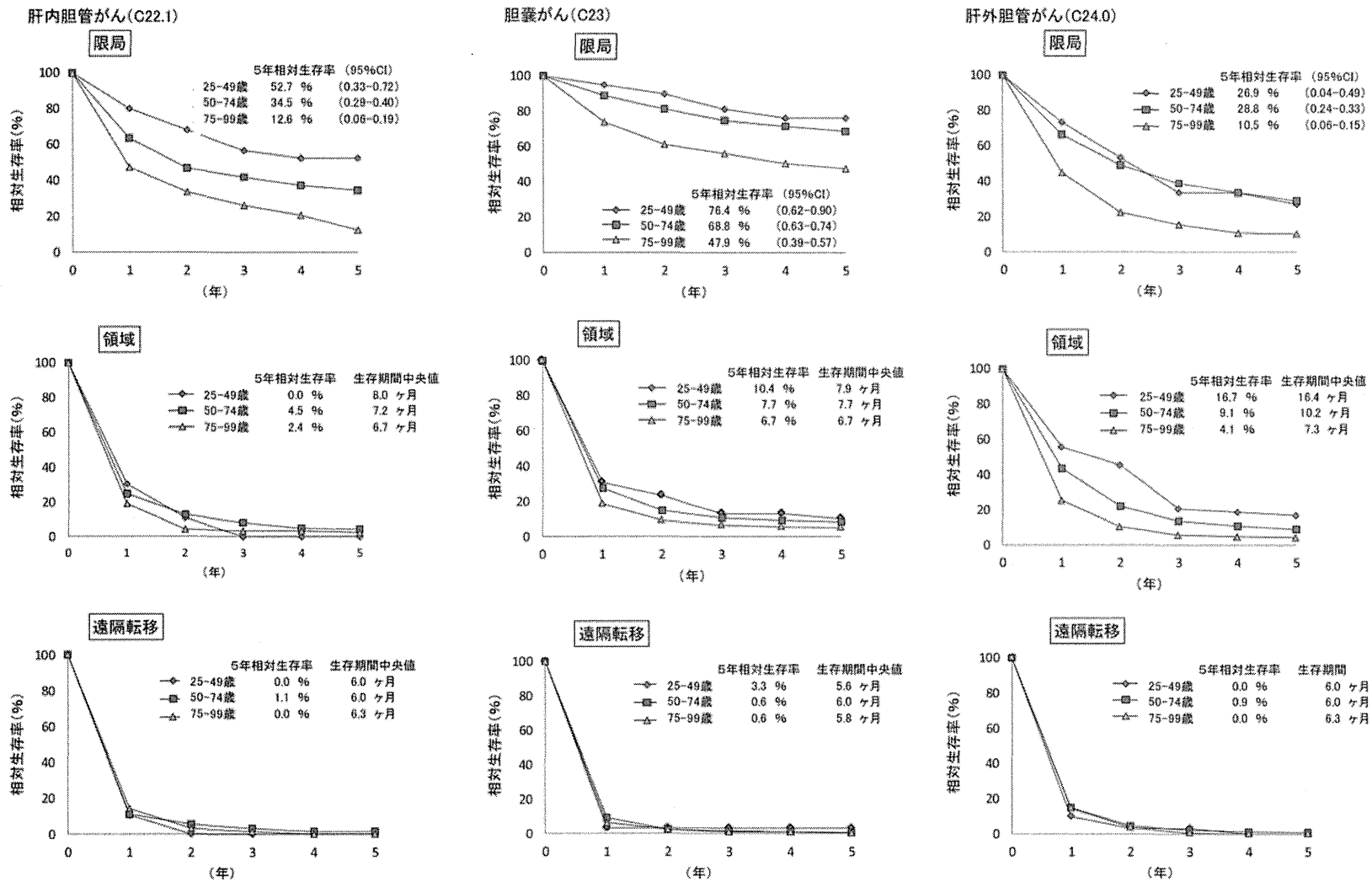


図 5-4. 部位別臨床進行度別 相対生存率曲線：1993-2005 年診断例 新発症届出患者 大阪

表 5-1. A 事業所から 1, 2, 5km 内外の住民における年齢調整標準化罹患比:2004-2007 年, 大阪府

性別	A 事業所からの距離	観察された罹患数	期待罹患数	SIR	95%信頼区間		p 値
男性	<1km	5	6.4	0.78	0.32	1.87	0.613
	1km+	1464	1498.4	0.98	0.93	1.03	0.374
	<2km	15	20.8	0.72	0.43	1.19	0.236
	2km+	1454	1484.0	0.98	0.93	1.03	0.436
	<5km	193	207.0	0.93	0.81	1.07	0.494
	5km+	1276	1297.9	0.98	0.93	1.04	0.543
女性	<1km	4	4.5	0.88	0.33	2.34	0.832
	1km+	923	944.1	0.98	0.92	1.04	0.492
	<2km	20	14.9	1.35	0.87	2.08	0.150
	2km+	907	933.8	0.97	0.91	1.04	0.381
	<5km	141	129.6	1.09	0.92	1.28	0.171
	5km+	786	819.0	0.96	0.89	1.03	0.249
男女計	<1km	9	11.1	0.81	0.42	1.55	0.572
	1km+	2387	2443.4	0.98	0.94	1.02	0.254
	<2km	35	36.3	0.96	0.69	1.34	0.944
	2km+	2361	2418.3	0.98	0.94	1.02	0.244
	<5km	334	335.0	1.00	0.90	1.11	0.677
	5km+	2062	2119.6	0.97	0.93	1.02	0.211

SIR: Poisson 回帰により推定された標準化罹患比

表 5-2. SaTScan の分析結果より p 値の小さい順に示されたクラスターの情報

性別	クラスター	A 事業所から の距離(km)	クラスターの半 径(km)	クラスターに含ま れる町字域の数	尤度比	p 値	観測数	期待数	相対危険
男性	1 (The most likely cluster)	8.2	0.0	1	8.599	0.196	2	0.01	199.4
	2	18.3	1.3	9	6.538	0.816	7	1.20	5.8
	3	8.6	1.2	21	6.441	0.855	23	9.83	2.4
	4	17.6	0.7	7	6.404	0.867	13	3.98	3.3
	5	27.5	0.6	3	5.781	0.973	6	1.00	6.0
	6	11.6	1.2	26	5.352	0.996	27	13.43	2.0
女性	1 (The most likely cluster)	11.7	0.7	4	8.933	0.157	10	1.81	5.6
	2	15.3	0.5	2	7.013	0.633	4	0.27	14.7
	3	4.3	1.7	22	6.896	0.661	30	14.09	2.2
	4	11.2	0.5	16	5.978	0.928	6	0.96	6.3
	5	10.0	1.3	25	5.829	0.953	15	5.37	2.8
	6	18.5	0.9	10	5.327	0.984	6	1.09	5.5
	7	23.0	0.6	4	5.240	0.997	4	0.44	9.0
	8	26.0	1.7	14	5.169	0.997	13	4.59	2.9
男女計	1 (The most likely cluster)	4.7	1.2	12	8.978	0.217	32	13.66	2.4
	2	8.2	0.0	1	8.167	0.348	2	0.01	160.4
	3	6.4	0.7	5	5.987	0.952	17	6.43	2.7
	4	8.8	1.9	39	5.777	0.965	59	36.76	1.6
	5	11.2	0.9	37	5.608	0.978	17	6.66	2.6
	6	23.0	0.6	4	5.230	0.996	6	1.11	5.4
	7	3.3	0.8	12	5.155	0.996	19	8.23	2.3

表 6-1

印刷組合の2010年7月～2012年3月の胆管がんを医療資源病名としてDPC退院した患者数と退院数

	(21-79歳)					(21-60歳)				
	本人		家族		Total	本人		家族		total
	M	F	M	F		M	F	M	F	
観察された患者数										
C22 (肝内胆管がん)	5	1		1	7	4				4
C24 (肝外胆管がん)	12			1	13	8				8
Total	17	1		2	20	12				12
観察された胆管がんを医療資源病名とするDPC退院数										
C22 (肝内胆管がん)	8	1	0	1	10	7				7
C24 (肝外胆管がん)	16	0	0	1	17	10				10
Total	24	1	0	2	27	17				17
予想された胆管がんを医療資源病名とするDPC退院数										
C22 (肝内胆管がん)	6.25	1.19	0.73	2.76	10.93	3.07	0.88	1.56	1.03	6.53
C24 (肝外胆管がん)	11.23	3.41	1.43	4.85	20.92	4.72	2.32	2.40	2.73	12.18
Total	17.49	4.59	2.16	7.61	31.85	7.79	3.20	3.95	3.76	18.71
標準化退院率比(観察数/予想数)*										
95% 信頼区間上限	3.64	12.06		3.57	2.16	8.74				3.11
C22 (肝内胆管がん)	1.28	0.84		0.36	0.91	2.28				1.07
95% 信頼区間下限	0.45	0.06		0.04	0.39	0.60				0.37
95% 信頼区間上限	3.05			1.78	1.54	6.32				1.90
C24 (肝外胆管がん)	1.42			0.21	0.81	2.12				0.82
95% 信頼区間下限	0.66			0.02	0.43	0.71				0.36
95% 信頼区間上限	2.54	1.89		1.25	1.42	5.09				1.75
全胆管がん	1.37	0.22		0.26	0.85	2.18				0.91
95% 信頼区間下限	0.74	0.03		0.06	0.51	0.93				0.47

*組合被保険者は74歳以下につき全年齢では過小評価となっている

表1 A測定 of 区分別にみた調査項目の比較

		区分 I	区分 II、区分 III	p value
		n=34	n=22	
		n (%), 平均値±標準偏差、中央値(最小値-最大値)		
単位作業場の広さ	広い(>120㎡)	9 (26.5%)	6 (27.3%)	1.000
	狭い(≤120㎡)	25 (73.5%)	16 (72.7%)	
取扱量	多い(>112kg/月)	28 (82.4%)	19 (86.4%)	1.000
	少ない(≤112kg/月)	6 (17.6%)	3 (13.6%)	
作業員数	単独	20 (58.8%)	16 (72.7%)	0.394
	複数	14 (41.2%)	6 (27.3%)	
気温 (°C)		23.8±3.7	22.5±6.4	0.339
湿度 (%)		43.2±11.6	45.8±12.4	0.420
気流 (m/sec)		0.3 (0.1-2.0)	0.4 (0.1-1.6)	0.467
局所排気装置	あり	19 (55.9%)	7 (31.8%)	0.103
	なし	15 (44.1%)	15 (68.2%)	
作業環境管理	適切	33 (97.1%)	15 (68.2%)	0.004*
	不適切	1 (2.9%)	7 (31.8%)	
業務内容	ろ過、混合、攪拌、加熱	10 (29.4%)	4 (18.2%)	0.529
	洗浄、払拭	24 (70.6%)	18 (81.8%)	

表2 B測定 of 区分別にみた調査項目の比較

		区分 I	区分 II、区分 III	p value
		n=40	n=16	
		n (%), 平均値±標準偏差、中央値(最小値-最大値)		
単位作業場の広さ	広い(>120㎡)	12 (30.0%)	3 (18.8%)	0.513
	狭い(≤120㎡)	28 (70.0%)	13 (81.2%)	
取扱量	多い(>112kg/月)	33 (82.5%)	14 (87.5%)	1.000
	少ない(≤112kg/月)	7 (17.5%)	2 (12.5%)	
作業員数	単独	22 (55.0%)	14 (87.5%)	0.031*
	複数	18 (45.0%)	2 (12.5%)	
気温 (°C)		23.8±4.9	21.8±5.0	0.173
湿度 (%)		44.1±11.6	44.6±12.8	0.871
気流 (m/sec)		0.3 (0.1-1.6)	0.3 (0.1-2.0)	0.749
局所排気装置	あり	20 (50.0%)	6 (37.5%)	0.554
	なし	20 (50.0%)	10 (62.5%)	
作業環境管理	適切	35 (87.5%)	13 (81.2%)	0.676
	不適切	5 (12.5%)	3 (18.8%)	
業務内容	ろ過、混合、攪拌、加熱	8 (20.0%)	6 (37.5%)	0.19
	洗浄、払拭	32 (80.0%)	10 (62.5%)	

表3 管理区分別にみた調査項目の比較

		管理区分1	管理区分2, 3	p value
		n=30	n=26	
		n (%), 平均値±標準偏差、中央値(最小値-最大値)		
単位作業場の広さ	広い(>120㎡)	9 (30.0%)	6 (23.1%)	0.763
	狭い(≤120㎡)	21 (70.0%)	20 (76.9%)	
取扱量	多い(>112kg/月)	24 (80.0%)	23 (88.5%)	0.481
	少ない(≤112kg/月)	6 (20.0%)	3 (11.5%)	
作業員数	単独	16 (53.3%)	20 (77.0%)	0.095
	複数	14 (46.7%)	6 (23.0%)	
気温 (°C)		23.4±4.6	23.1±5.4	0.811
湿度 (%)		43.0±11.6	45.6±12.2	0.428
気流 (m/sec)		0.3 (0.1-1.6)	0.35 (0.1-2.0)	0.720
局所排気装置	あり	16 (53.3%)	10 (38.5%)	0.295
	なし	14 (46.7%)	16 (61.5%)	
作業環境管理	適切	29 (96.7%)	19 (73.1%)	0.019*
	不適切	1 (3.3%)	7 (26.9%)	
業務内容	ろ過、混合、攪拌、加熱	7 (23.3%)	7 (26.9%)	0.768
	洗浄、払拭	23 (76.7%)	19 (73.1%)	

表 7-1.2.3

Table 1. Basic information used to estimate exposure concentrations of 1,2-dichloropropane and dichloromethane.

Plant	Worker	Calendar years employed as a printing worker	Printing room					Ink removal operation				Chemicals used for ink removal operation				
			No.	Volume (m ³)	Ventilation rate (m ³ /hr)	Frequency of air exchange (hr ⁻¹)	Amount of 1,2-DCP (g/hr)	Amount of DCM (g/hr)	Printing machine	r (m)	β (m ³ /hr)	Amount of 1,2-DCP (g/hr)	Amount of DCM (g/hr)	Ink removal from blanket	Ink removal from ink roll	
I	A	1988–1994		NI	NI	---	---	---	Rotary offset	NI		---	---	1,1,1-TCE		
		1995–1998	1	1260	3690	2.9	630	< 1		0.5	570	1100	< 4	1,2-DCP, DCM	MS Naphtha	
		1999–2011					660–710	< 1	Sheet-fed offset			630–900	< 4			
	B	1992–1994		NI	NI	---	---	---	Rotary offset	NI		---	---	1,1,1-TCE		
		1995	1	1260	3690	2.9	630	< 1		0.5	570	1100	< 4			
		1996–2001					360	< 1	Sheet-fed relief			900	< 4	1,2-DCP, DCM	MS Naphtha	
		2002–2004	2	570	1960	3.4	360	< 1	Rotary relief	0.85	1630	1800	< 4			
			2005–2011				320–360	< 1	Rotary offset	0.5	570	630–700	< 4			
	II	C	1970–1973 1975–1985		NI	NI	---	---	---		NI		---	---	Gasoline	
			1986–1990			3020	17.8	230	270				330	400	1,2-DCP, DCM	Kerosen MO
1990–1992							230	270	Flatbed offset (proof-printing)			330	400			
1993			3	170			230	270		0.5	570	330	400	1,2-DCP, DCM, MS		
1994–1995					1790	10.5	240–270	280–310				560–720	670–830			
D		1996–1998					280–480	56				720–1200	170	1,2-DCP, DCM, DCFE, MS		
		1992					230	270				330	400	1,2-DCP, DCM		
		1993–1995					230–270	270–310				330–430	400–500	1,2-DCP, DCM, MS		
		1996–1998	3	170	1790	10.5	280–480	56	Flatbed offset (proof-printing)	0.5	570	430–730	100	1,2-DCP, DCM, DCFE, MS	Kerosen MO	
		1999					470	0				700	0	1,2-DCP, DCFE		
		2000–2004				470–580	0				700–830	0	1,2-DCP			
III	E F	1980–1984		NI	NI	---	---	---		NI		---	---	Gasoline		
		1985–1987	5	150	480	3.2	390	160				350	140			
		1988–1991	6	750	2400	3.2	390	160	Flatbed offset (proof-printing)	0.5	570	350	140	1,2-DCP, DCM, 1.1.1-TCE	Kerosen	
		1991–1992					390	160				350	140			
		1993–1995	7	340	1090	3.2	320	370				280	320	1,2-DCP, DCM, MS		

NI: no information, r: radius of near field, β: air exchange rate between near-field and far-field = $0.1 \times 3600 \times 2\pi r^2$, 1,2-DCP: 1,2-dichloropropane, DCM: dichloromethane, 1,1,1-TCE: 1,1,1-trichloroethane, DCFE: 1,1-dichloro-1-fluoroethane, MS: mineral spirit, MO: mineral oil

Table 2. Estimated working environment concentrations of 1,2-dichloropropane and dichloromethane in printing rooms, exposure concentrations during ink removal operation and shift time-weighted averages (TWAs)

Plant	Worker	Calendar years employed as a printing worker	Printing room		Printing machine	Ink removal operation			Shift TWAs				
			No.	1,2-DCP (ppm)		DCM (ppm)	Duration (hr)	1,2-DCP (ppm)	DCM (ppm)	Working hours (hr)	1,2-DCP (ppm)	DCM (ppm)	
I	A	1988–1994		---	---	Rotary offset	NI	---	---	NI	---	---	
		1995–1998	1	37	< 1		1.5	490	< 3	10	100	< 1	
		1999–2011		39–42	< 1		Sheet-fed offset	3.5	280–400	< 3		120–170	< 1
	B	1992–1994		---	---	Rotary offset	NI	---	---	NI	---	---	
		1995	1	37	< 1		1.5	490	< 3	10	100	< 1	
		1996–2001		40	< 1		Sheet-fed relief	2	440	< 3		120	< 1
		2002–2004	2	40	< 1		Rotary relief	1	440	< 3		80	< 1
			2005–2011		35–40	< 1	Rotary offset	2.5	310–350	< 3		100–120	< 1
	II	C	1970–1973 1975–1985		---	---	Flatbed offset (proof-printing)	NI	---	---	NI	---	---
			1986–1990		17	25			150	240		62	98
1990–1992				28	43	3		170	270		75	120	
1993			3	28	43			170	270	9	75	120	
1994–1995				30–32	45–50	1.8		280–360	450–560		80–99	130–150	
			1996–1998		34–58	9	360–620	110		100–170	29		
D		1992		28	43	Flatbed offset (proof-printing)		170	270		75	120	
		1993–1995		28–32	43–50			170–220	270–340		75–94	120–150	
		1996–1998	3	34–58	9		3	220–370	67	9	95–160	28	
		1999		56	0			350	0		160	0	
	2000–2004		56–70	0			350–420	0		160–190	0		
		2005–2008	4	92	0		410	0		200	0		
III	E F	1980–1984		---	---	Flatbed offset (proof-printing)	NI	---	---	NI	---	---	
		1985–1987	5	180	98			290	160		240	130	
		1988–1991	6	35	20		6.5	160	91	11.5	110	60	
		1991–1992		78	43			200	110		150	82	
		1993–1995	7	64	97			160	250		120	180	

NI: no information, 1,2-DCP: 1,2-dichloropropane, DCM: dichloromethane

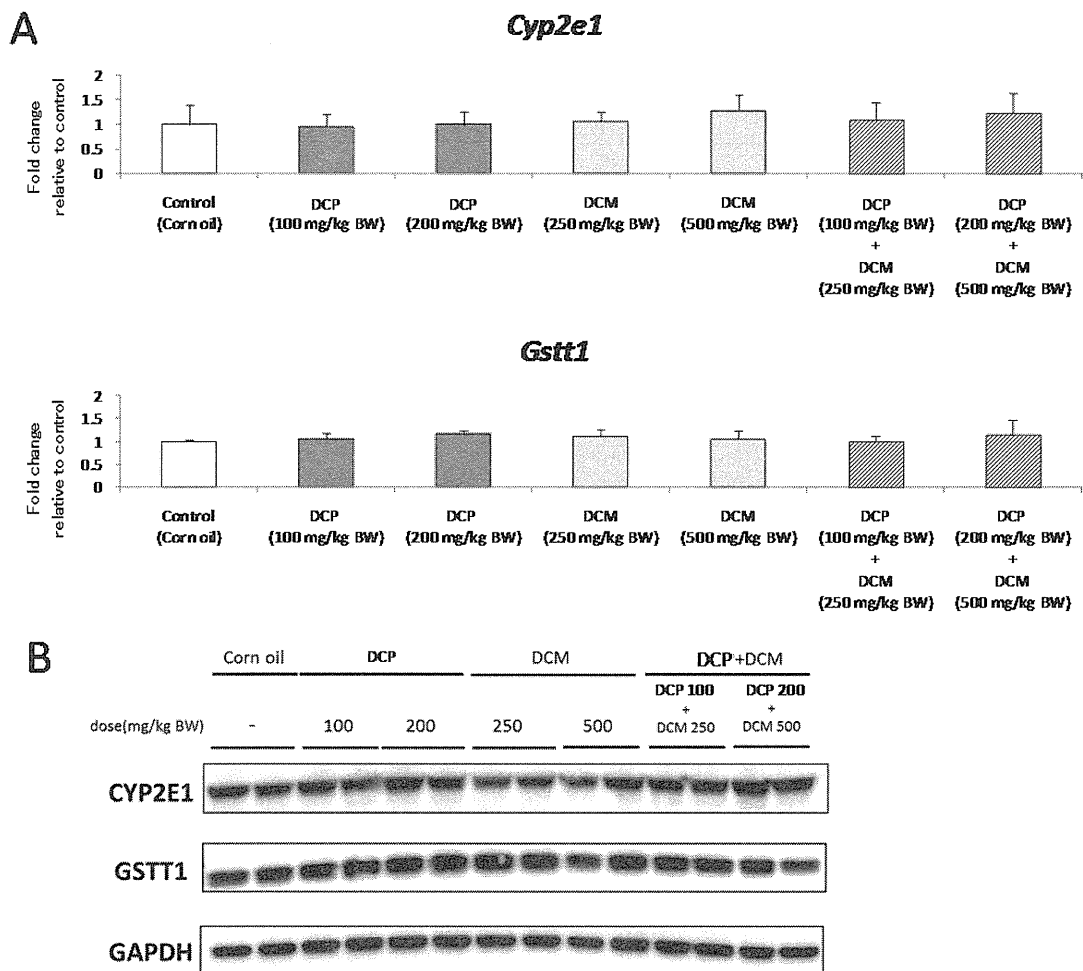


Figure 1 (A) Changes in the mRNA level of DCP and DCM metabolic enzyme genes, *Cyp2e1* and *Gstt1*, in the liver of *gpt* delta rats treated with DCP, DCM or their combination for 4 weeks. Each value is the mean \pm SD of data from seven or eight rats. Data were normalized with GAPDH mRNA levels (B) Western blotting analysis of CYP2E1 and GSTT1 in the liver of *gpt* delta rats treated with DCP, DCM or their combination for 4 weeks.

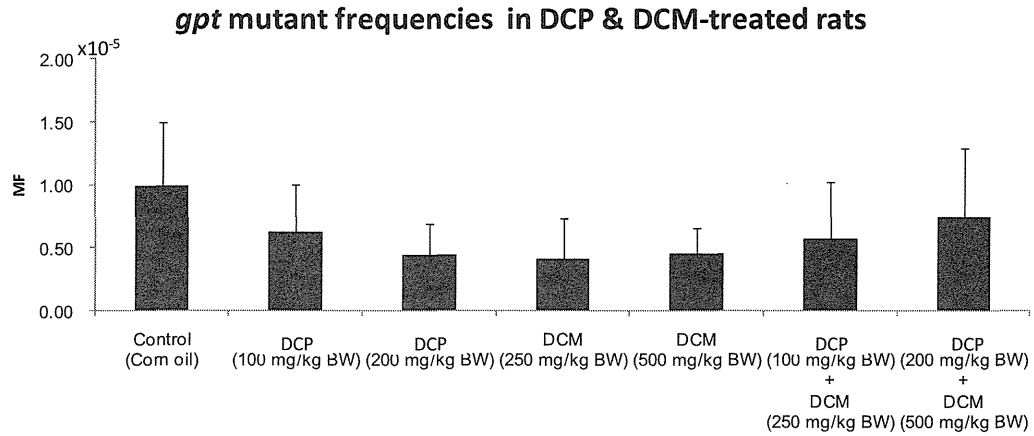
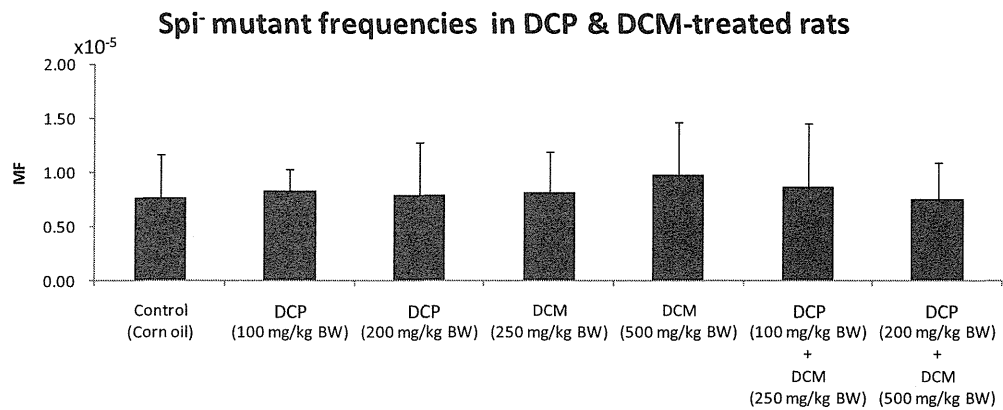
A**B**

Figure 2 (A) *gpt* mutant frequencies, (B) *Spi* mutant frequencies in the liver of *gpt* delta rats treated with DCP, DCM or their combination for 4 weeks. The values represent the means of experiments \pm SD.

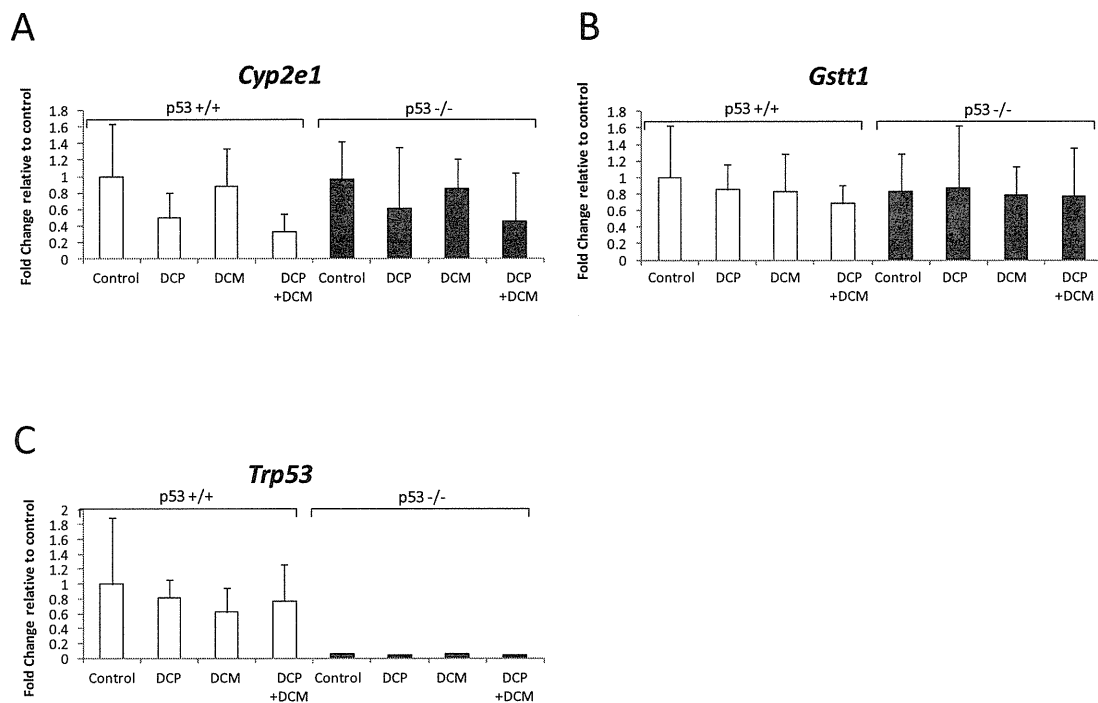


Figure 3 Changes in the mRNA level of DCP and DCM metabolic enzyme genes, (A) *Cyp2e1* and (B) *Gstt1*, in the liver of *gpt* delta rats treated with DCP, DCM or their combination for 4 weeks. In addition, (C) *Trp53*. Each value is the mean \pm SD of data from four or five mice. Data were normalized with GAPDH mRNA levels.

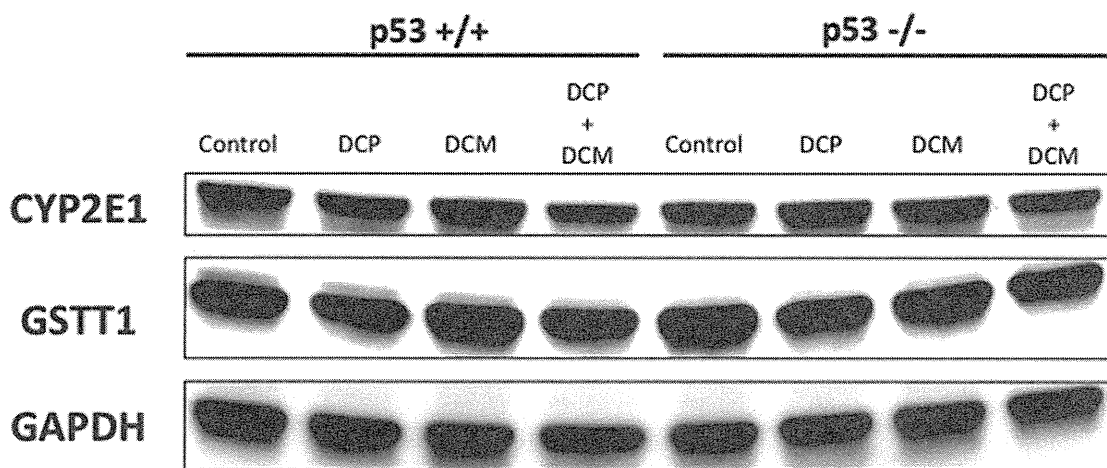


Figure 4 Western blotting analysis of CYP2E1 and GSTT1 in the liver of p53-proficient and -deficient *gpt* delta mice treated with DCP, DCM or their combination for 4 weeks.

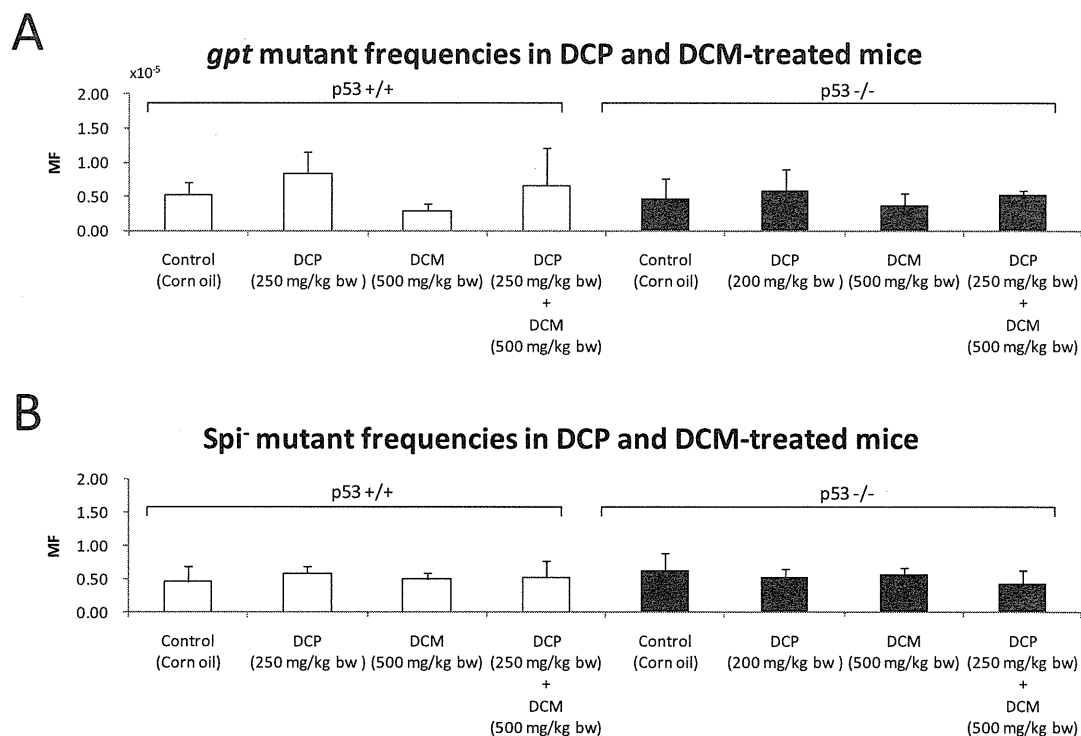


Figure 5 (A) *gpt* mutant frequencies, (B) Spi- mutant frequencies in the liver of p53-proficient and -deficient *gpt* delta mice treated with DCP, DCM or their combination for 4 weeks. The values represent the means of experiments \pm SD.

Table I Terminal body weight and liver weight of male *gpt* delta rats treated with DCP and DCM for 4 weeks.

Group	Terminal body weight (g)	Liver weight	
		Absolute (g)	Relative (g %)
Control (Corn oil)	196.4 ± 12.8	5.83 ± 0.58	2.96 ± 0.16
DCP 100 mg / kg BW	188.3 ± 11.0	5.33 ± 0.27	2.93 ± 0.11
DCP 200 mg / kg BW	180.0 ± 12.5	5.54 ± 0.43	3.18 ± 0.20
DCM 250 mg / kg BW	208.6 ± 12.8	5.86 ± 0.50	2.93 ± 0.12
DCM 500 mg / kg BW	207.8 ± 10.1	5.89 ± 0.27	2.96 ± 0.08
DCP 100 + DCM 250 mg / kg BW	192.5 ± 8.2	5.56 ± 0.32	2.98 ± 0.09
DCP 200 + DCM 500 mg / kg BW	188.4 ± 10.5	5.74 ± 0.22	3.16 ± 0.11

Table II Blood chemistry study of male *gpt* delta rats treated with DCP and DCM for 4 weeks.

Treatment	Control (Corn oil)	DCP (mg / kg BW)		DCM (mg / kg BW)		DCP + DCM (mg / kg BW)	
		100	200	250	500	100 + 250	200 + 500
TP (g/dL)	5.7 ± 0.1	5.6 ± 0.1	5.8 ± 0.2	5.6 ± 0.1	5.8 ± 0.1	5.6 ± 0.1	5.6 ± 0.2
Alb (g/dL)	4.2 ± 0.1	4.1 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.1	4.2 ± 0.1
A/G	2.8 ± 0.1	2.8 ± 0.2	2.9 ± 0.2	3.0 ± 0.2	3.0 ± 0.2	2.9 ± 0.1	3.0 ± 0.2
Glucose (mg/dL)	167 ± 15	159 ± 33	151 ± 13	144 ± 15	135 ± 14*	139 ± 13	141 ± 16
Bil (mg/dL)	0.04 ± 0.01	0.04 ± 0.01	0.06 ± 0.01**	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01
T-Cho (mg/dL)	59 ± 4	49 ± 5**	43 ± 4**	54 ± 3	54 ± 3	48 ± 6**	40 ± 8**
TG (mg/dL)	65 ± 5	38 ± 6*	30 ± 8**	55 ± 32	46 ± 8	35 ± 11**	29 ± 8**
γGTP (IU/L)	<3	<3	<3	<3	<3	<3	<3
AST (IU/L)	67 ± 4	74 ± 5	74 ± 5	68 ± 5	69 ± 4	72 ± 4	67 ± 4
ALT (IU/L)	41 ± 5	34 ± 2**	27 ± 3**	40 ± 1	40 ± 4	34 ± 4**	25 ± 2**
ALP (IU/L)	1006 ± 101	1045 ± 108	952 ± 109	929 ± 111	920 ± 126	975 ± 139	871 ± 89
BUN (mg/dL)	19 ± 2	18 ± 1	20 ± 2	19 ± 2	18 ± 2	19 ± 2	19 ± 3
Cre (mg/dL)	0.28 ± 0.02	0.29 ± 0.02	0.27 ± 0.03	0.28 ± 0.03	0.28 ± 0.01	0.29 ± 0.03	0.28 ± 0.02
Ca (mg/dL)	10.2 ± 0.2	9.9 ± 0.2	10.2 ± 0.2	10.0 ± 0.3	10.1 ± 0.2	10.1 ± 0.2	10.2 ± 0.2
IP (mg/dL)	7.0 ± 0.2	6.9 ± 0.2	6.9 ± 0.3	7.3 ± 0.2	7.2 ± 0.3	7.3 ± 0.3	7.6 ± 0.3**
Na (mg/dL)	143 ± 0	144 ± 1	145 ± 1	143 ± 1	144 ± 0	144 ± 1	144 ± 0
K (mg/dL)	4.6 ± 0.2	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.2	4.5 ± 0.1	4.6 ± 0.2	4.7 ± 0.2
Cl (mg/dL)	104 ± 1	105 ± 1	105 ± 1	103 ± 1	103 ± 1	105 ± 1	104 ± 1

Each value represents the mean ± SD. TP, total protein; Alb, albumin; Bil, bilirubin; T-Cho, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cre, creatinine. Significantly different from the vehicle control group at *P < 0.05 and **P < 0.01.

Table III Histopathological findings of male *gpt* delta rats treated with DCP and DCM for 4 weeks.

Treatment	Control (Corn oil)	DCP (mg/kg BW)		DCM (mg/kg BW)		DCP + DCM (mg/kg BW)	
		100	200	250	500	100 + 250	200 + 500
Organs and findings	No. of animals	7	7	7	7	7	8
Liver							
Eosinophilic change	0	0	0	1	0	0	2
Cell infiltration	6	6	7	7	7	7	8
Microgranuloma	2	3	1	5	5	5	4
Single cell necrosis	3	3	4	3	1	3	2
Karyocytomegaly	0	0	0	0	1	0	0
Mitosis	3	0	0	2	1	0	0

Table IV *gpt* MFs in the liver of male *gpt* delta rats treated with 1,2-dichloropropane and dichloromethane for 4 weeks.

Treatment	Animal No.	Cm ^R colonies (x10 ⁵)	6-TG ^R and Cm ^R colonies	Mutant Frequency (x10 ⁻⁵)	Mean ± S.D.
Control (Corn oil)	1	7.8	4	0.51	1.0 ± 0.5
	2	6.0	10	1.67	
	3	6.4	4	0.62	
	4	5.9	8	1.35	
	5	7.2	6	0.83	
DCP (100 mg/kg BW)	8	7.9	3	0.38	0.63 ± 0.38
	9	5.8	4	0.69	
	10	6.9	3	0.44	
	11	8.3	3	0.36	
	12	4.0	5	1.26	
DCP (200 mg/kg BW)	15	6.1	3	0.49	0.47 ± 0.23
	16	5.2	1	0.19	
	17	8.5	4	0.47	
	18	10.8	3	0.28	
	19	3.6	3	0.82	
DCM (250 mg/kg BW)	22	5.1	5	0.97	0.41 ± 0.33
	23	9.1	1	0.31	
	24	6.4	2	0.11	
	25	10.3	3	0.29	
	26	8.1	3	0.37	
DCM (500 mg/kg BW)	29	6.9	2	0.29	0.46 ± 0.20
	30	9.0	7	0.78	
	31	5.9	2	0.34	
	32	7.7	4	0.52	
	33	5.4	2	0.37	
DCP (100 mg/kg BW) + DCM (250 mg/kg BW)	36	6.9	1	0.15	0.70 ± 0.42
	37	5.2	6	1.16	
	38	7.1	5	0.70	
	39	9.0	7	0.78	
DCP (200 mg/kg BW) + DCM (500 mg/kg BW)	40	9.5	1	0.11	0.75 ± 0.54
	43	3.1	4	1.31	
	44	7.5	10	1.33	
	45	11.6	6	0.52	
	46	6.7	3	0.45	
	47	7.9	1	0.13	

Table V Spi-MFs in the liver of male *gpt* delta rats treated with 1,2-dichloropropane and dichloromethane for 4 weeks.

Treatment	Animal No.	Plaques within XL-1 Blue MRA ($\times 10^5$)	Plaques within WL95 (P2)	Mutant Frequency ($\times 10^{-5}$)	Mean \pm S.D.
Control (Corn oil)	1	18.0	4	0.22	0.77 \pm 0.40
	2	15.4	12	0.78	
	3	17.4	14	0.81	
	4	9.7	7	0.72	
	5	12.0	16	1.34	
DCP (100 mg/kg BW)	8	9.7	5	0.51	0.82 \pm 0.20
	9	13.5	12	0.89	
	10	9.0	7	0.78	
	11	14.8	13	0.88	
	12	3.8	4	1.06	
DCP (200 mg/kg BW)	15	7.7	3	0.39	0.80 \pm 0.48
	16	6.0	4	0.66	
	17	10.0	5	0.50	
	18	18.8	30	1.59	
	19	6.0	5	0.83	
DCM (250 mg/kg BW)	22	12.2	7	0.57	0.82 \pm 0.37
	23	10.6	12	1.13	
	24	10.6	4	0.38	
	25	17.6	22	1.25	
	26	7.7	6	0.78	
DCM (500 mg/kg BW)	29	8.6	6	0.70	0.98 \pm 0.49
	30	19.6	10	0.51	
	31	10.3	7	0.68	
	32	9.7	13	1.34	
	33	6.0	10	1.66	
DCP (100 mg/kg BW) + DCM (250 mg/kg BW)	36	10.1	3	0.30	0.85 \pm 0.68
	37	7.8	10	1.28	
	38	12.6	3	0.24	
	39	10.7	17	1.59	
	40	16.3	15	0.92	
DCP (200 mg/kg BW) + DCM (500 mg/kg BW)	43	9.0	3	0.33	0.76 \pm 0.33
	44	12.0	8	0.67	
	45	13.0	8	0.62	
	46	12.8	14	1.10	
	47	15.6	17	1.09	

Table VI Terminal body weight and liver weight of male p53-proficient and -deficient *gpt* delta mice treated with DCP and DCM for 4 weeks.

Genotype	Treatment	Terminal body weight (g)		Liver weight	
				Absolute (g)	Relative (g %)
p53-proficient	Control (Corn oil)	24.5 ± 1.3		1.1 ± 0.2	4.5 ± 0.4
	DCP	25.7 ± 1.5		1.3 ± 0.1	5.2 ± 0.3
	DCM	25.3 ± 1.5		1.2 ± 0.1	4.6 ± 0.1
	DCP + DCM	26.3 ± 1.7		1.5 ± 0.1**	5.6 ± 0.2*
p53-deficient	Control (Corn oil)	25.8 ± 2.1		1.1 ± 0.1	4.1 ± 0.4
	DCP	26.9 ± 1.1		1.4 ± 0.2###	5.2 ± 0.6#
	DCM	25.5 ± 1.6		1.0 ± 0.1	4.1 ± 0.5
	DCP + DCM	27.0 ± 1.4		1.3 ± 0.2	4.9 ± 0.9

*,** P < 0.05 and P < 0.01 vs. control between p53-proficient samples(Tukey's test).

#,## P < 0.05 and P < 0.01 vs. control between p53-deficient samples(Tukey's test).

Table VII Blood chemistry study of male p53-proficient and -deficient *gpt* delta mice treated with DCP and DCM for 4 weeks.

Genotype	p53-proficient				p53-deficient				
	Treatment	Control (Corn oil)	DCP	DCM	DCP + DCM	Control (Corn oil)	DCP	DCM	DCP + DCM
TP (g/dL)		5.2 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	5.1 ± 0.3	4.7 ± 0.4	4.7 ± 0.3	4.8 ± 0.4	4.7 ± 0.4
Alb (g/dL)		3.5 ± 0.2	3.3 ± 0.1	3.6 ± 0.2	3.5 ± 0.2	3.0 ± 0.4	3.1 ± 0.1	3.3 ± 0.4	3.2 ± 0.3
A/G		2.1 ± 0.3	2.0 ± 0.1	2.6 ± 0.5	2.3 ± 0.2	1.9 ± 0.4	2.0 ± 0.1	2.1 ± 0.2	2.1 ± 0.3
Glucose (mg/dL)		164 ± 37	166 ± 36	184 ± 22	169 ± 27	176 ± 61	186 ± 29	137 ± 28	199 ± 23
Bil (mg/dL)		0.09 ± 0.01	0.14 ± 0.01	0.10 ± 0.02	0.12 ± 0.02	0.07 ± 0.01	0.12 ± 0.04	0.09 ± 0.04	0.14 ± 0.04###
T-Chol (mg/dL)		112 ± 11	119 ± 7	110 ± 5	109 ± 11	110 ± 18	116 ± 19	103 ± 22	109 ± 25
TG (mg/dL)		61 ± 55	75 ± 19	35 ± 5	109 ± 29	32 ± 21	59 ± 25	34 ± 32	76 ± 54
γGTP (IU/L)		>6	>6	>6	>6	>6	>6	>6	>6
AST (IU/L)		45 ± 9	66 ± 14	52 ± 17	66 ± 23	46 ± 11	39 ± 5	80 ± 88	103 ± 69
ALT (IU/L)		17 ± 3	23 ± 8	18 ± 2	41 ± 16	14 ± 5	18 ± 7	22 ± 22	33 ± 16
ALP (IU/L)		265 ± 21	227 ± 22	202 ± 57	215 ± 13	220 ± 55	214 ± 43	217 ± 47	203 ± 39
BUN (mg/dL)		25 ± 12	13 ± 2**	17 ± 2	17 ± 2	18 ± 3	14 ± 4	15 ± 2	16 ± 3
PL (mg/dL)		206 ± 24	225 ± 17	203 ± 14	229 ± 25	197 ± 29	222 ± 26	186 ± 37	201 ± 52
Ca (mg/dL)		9.5 ± 0.7	9.0 ± 0.3	9.5 ± 0.6	9.7 ± 0.3	8.8 ± 0.5	9.0 ± 0.1	9.0 ± 0.9	11.0 ± 2.8#
IP (mg/dL)		6.8 ± 0.6	6.0 ± 1.7	7.3 ± 0.9	6.8 ± 1.6	7.4 ± 0.6	6.1 ± 1.1	7.8 ± 1.0	7.1 ± 0.6
Na (mEQ/L)		157 ± 4	153 ± 2	156 ± 3	155 ± 1	155 ± 1	153 ± 1	157 ± 3	155 ± 2
K (mEQ/L)		4.6 ± 0.8	4.7 ± 0.3	4.0 ± 0.1	4.2 ± 0.4	4.1 ± 0.2	4.5 ± 0.3	4.3 ± 0.4	4.5 ± 0.7
Cl (mEQ/L)		103 ± 4	107 ± 2	104 ± 6	104 ± 6	108 ± 5	110 ± 1	103 ± 7	104 ± 8

Each value represents the mean ± SD. TP, total protein; Alb, albumin; Bil, bilirubin; T-Chol, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; PL, phospholipids.

Significantly different from the p53-proficient control group at *P < 0.05 and **P < 0.01, -deficient control group at #P < 0.05 and ##P < 0.01.

Table VIII Histopathological findings of male p53-proficient and -deficient *gpt* delta mice treated with DCP and DCM for 4 weeks.

Organ and findings	Genotype	p53-proficient				p53-deficient				
		Treatment	Control (Corn oil)	DCP	DCM	DCP + DCM	Control (Corn oil)	DCP	DCM	DCP + DCM
		No. of animals	4	4	4	5	8	6	7	7
Liver										
Glycogen deposition		0	4*	0	5*	0	6###	0	6###	
Microgranuloma		4	2	4	4	8	6	6	7	
Hydrophic degeneration		0	0	1	3	0	0	0	1	
Focal necrosis		0	0	0	0	1	0	0	0	
Single cell necrosis		0	0	0	0	0	0	0	1	
Karyocytomegaly		0	0	0	0	0	4#	0	1	
Malignant lymphoma		0	0	0	0	0	0	1	0	

Significantly different from the p53-proficient control group at *P < 0.05 and **P < 0.01, -deficient control group at #P < 0.05 and ##P < 0.01.

Table IX *gpt* MFs in the liver of male p53 KO *gpt* delta mice treated with 1,2-dichloropropane and dichloromethane for 4 weeks.

Genotype	Treatment	Animal No.	Cm ^R colonies (x10 ⁶)	6-TG ^R and Cm ^R colonies	Mutant Frequency (x10 ⁻⁵)	Mean ± S.D.
p53 +/+	Control (Corn oil)	1	11.4	9	0.79	0.53 ± 0.18
		2	14.4	7	0.49	
		3	23.8	9	0.38	
		5	17.3	8	0.46	
	DCP (250 mg/kg bw)	6	11.7	12	1.03	0.85 ± 0.31
		7	20.1	17	0.85	
		8	17.0	7	0.41	
		9	15.6	17	1.09	
		10	16.4	7	0.43	
	DCM (500 mg/kg bw)	11	29.2	5	0.17	0.30 ± 0.11
		12	38.2	10	0.26	
		13	18.4	6	0.33	
		14	18.9	15	0.79	
	DCP (250 mg/kg bw) +	15	8.3	13	1.56	0.66 ± 0.53
		16	21.2	10	0.47	
		17	29.1	9	0.31	
		18	17.1	3	0.18	
	p53 -/-	Control (Corn oil)	19	23.2	8	0.35
20			14.9	13	0.87	
21			17.2	12	0.70	
22			30.9	5	0.16	
23			20.3	7	0.34	
DCP (250 mg/kg bw)		28	29.7	9	0.30	0.59 ± 0.32
		29	8.6	9	1.05	
		31	16.3	7	0.43	
		32	6.3	5	0.79	
		33	19.4	7	0.36	
DCM (500 mg/kg bw)		35	24.3	13	0.54	0.37 ± 0.18
		36	29.7	17	0.57	
		37	27.3	9	0.33	
		39	37.2	7	0.19	
		40	17.5	4	0.23	
DCP (250 mg/kg bw) +		44	27.3	16	0.59	0.54 ± 0.45
		45	7.0	4	0.57	
		46	21.0	11	0.52	
	47	25.5	12	0.47		
DCM (500 mg/kg bw)	48	14.4	8	0.55		

Table X Spi- MFs in the liver of male p53 KO *gpt* delta mice treated with 1,2-dichloropropane and dichloromethane for 4 weeks.

Genotype	Treatment	Animal No.	Plaques within XL-1 Blue MRA (x10 ⁶)	Plaques within WL95 (P2)	Mutant Frequency (x10 ⁻⁵)	Mean ± S.D.
p53 +/+	Control (Corn oil)	1	20.8	6	0.29	0.45 ± 0.25
		2	43.7	14	0.32	
		3	15.8	13	0.82	
		4	44.8	17	0.38	
		5	20.1	10	0.50	
	DCP (250 mg/kg bw)	6	20.1	10	0.50	0.59 ± 0.10
		7	31.7	16	0.51	
		8	29.5	19	0.64	
		9	17.1	12	0.70	
	DCM (500 mg/kg bw)	10	29.5	17	0.58	0.49 ± 0.09
		11	30.4	11	0.36	
		12	60.8	30	0.49	
		13	29.7	16	0.54	
		14	22.5	9	0.40	
	DCP (250 mg/kg bw) + DCM (500 mg/kg bw)	15	23.6	17	0.72	0.52 ± 0.25
		16	31.2	10	0.32	
		17	61.4	19	0.31	
		18	15.1	13	0.86	
p53 -/-	Control (Corn oil)	19	42.3	17	0.40	0.63 ± 0.25
		20	20.5	21	1.02	
		21	45.9	20	0.44	
		22	49.4	26	0.53	
		23	37.3	29	0.78	
	DCP (250 mg/kg bw)	24	52.3	26	0.50	0.52 ± 0.13
		25	19.4	13	0.67	
		26	15.9	8	0.50	
		27	30.8	19	0.62	
		28	15.4	5	0.32	
	DCM (500 mg/kg bw)	29	35.7	23	0.64	0.58 ± 0.10
		30	27.9	13	0.47	
		31	36.4	17	0.47	
		32	22.0	15	0.68	
		33	25.6	16	0.63	
	DCP (250 mg/kg bw) + DCM (500 mg/kg bw)	34	39.2	15	0.38	0.43 ± 0.20
		35	14.8	5	0.34	
		36	28.4	14	0.49	
37		28.3	21	0.74		
38		24.4	5	0.21		

Table.1 生存率、最終体重、肝重量、飲水量および摂餌量

	BOP initiation	1,2-DCP (mg/kg b.w.)	Effective no. of animals	Final body weight (g)	Absolute liver weight (g)	Relative liver weight (%)	Average water consumption (g/day/animal)	Average food consumption (g/day/animal)
Week 17								
1	+	0	9	168 ± 14	N.D.	N.D.	8.1	7.3
2	+	62.5	9	173 ± 11	N.D.	N.D.	8.1	7.3
3	+	125	9	146 ± 12*	N.D.	N.D.	7.5	6.7
Week 19								
1	+	0	15	170 ± 9	8.1 ± 0.7	4.8 ± 0.3	7.8	7.3
2	+	62.5	14 ^a	173 ± 12	8.2 ± 1.1	4.7 ± 0.4	8.1	7.4
3	+	125	15	155 ± 12*	7.4 ± 0.8	4.7 ± 0.3	7.8	6.8
4	-	125	9	166 ± 14	7.7 ± 0.9	4.6 ± 0.2	7.5	7.4
5	-	0	6	181 ± 13	8.5 ± 1.1	4.7 ± 0.4	7.8	7.6

N.D. not determined

^a 第12週時に1匹死亡、集計に含めない

* 有意差有り (p<0.01、vs. BOP単独投与群)

Table.2 肝内胆管上皮における前がん病変および腫瘍性病変

	BOP initiation	1,2-DCP (mg/kg b.w.)	Effective no. of animals	Atypical biliary hyperplasia		Cholangioma	
				Incidence (%)	Multiplicity (No./hamster)	Incidence (%)	Multiplicity (No./hamster)
Week 17							
1	+	0	9	2 (22%)	0.44 ± 0.88	0	0
2	+	62.5	9	3 (33%)	0.78 ± 1.20	0	0
3	+	125	9	1 (11%)	0.11 ± 0.33	0	0
Week 19							
1	+	0	15	7 (47%)	0.80 ± 0.94	0	0
2	+	62.5	14 ^a	6 (43%)	0.93 ± 1.44	1 (7.1%)	0.07±0.27
3	+	125	15	8 (53%)	0.73 ± 1.02	0	0
4	-	125	9	0	0	0	0
5	-	0	6	0	0	0	0

a 第12週時に1匹死亡、集計に含めない